Dengue, Vaccination and Vector Control

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Abstract

Dengue is a vector borne disease transmitted by the *Aedes Aegpti* mosquito. The dengue virus is capable of causing dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) potentially fatal forms of the disease with worldwide morbidity and mortality that has been increasing annually. Many strategies have been proposed to reduce the burden of this disease. Treatment for the various forms of the disease is supportive. Much research has been devoted to developing a vaccine to prevent this disease, but a safe and effective vaccine is not currently available. The research and difficulties surrounding the search for a vaccine will be discussed in this paper. Various forms of vector control have also been attempted over the past century with varying degrees of success. The history of the disease and vector control will be explored.

This disease has been especially harmful to areas like Puerto Rico where the cost of dengue over the past ten years has been $250 million. This paper will include a systematic review of the literature to determine a feasible, cost effective and sustainable policy for long-term reduction of dengue-related morbidity and mortality in Puerto Rico.

Focus of Paper/Question

In 1991 Gubler et al[1] published a paper recommending a new policy to reduce morbidity and mortality caused by Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) in Puerto Rico. The author outlines the available options at the time the article was published. The options were as follows: "*Aedes aegypti* eradication, ultra-low-volume (ULV) insecticide application, regulation of air travel, development and use of dengue vaccines, preventive measures keyed to improved surveillance, and routine mosquito control efforts". [1] Gubler et al[1] explains how the only viable options in 1991 are the last two: improved surveillance and routine mosquito control efforts and a five-component program is proposed that elaborates on these two options. The program includes 1. proactive surveillance; 2. rapid-response emergency vector control; 3. long-term, integrated community-based mosquito control; 4. education of the medical community; 5. an emergency hospitalization plan. This paper will review the literature from the time of the publishing of this article (1991) to the present to determine what policy has the best potential for limiting or decreasing morbidity and mortality from Dengue virus infection in Puerto Rico today.[1]

BACKGROUND

Epidemiology of the Disease

Many aspects of Dengue virus infection have led to its emergence in recent years as a threat to human health that is increasingly difficult to control in areas like Puerto Rico where epidemics occur. Throughout the world's tropical regions the epidemics of Dengue are becoming larger and more frequent.[2]

There is an estimated worldwide prevalence of 50-100 million cases of Dengue fever, 250-500 thousand cases of Dengue hemorrhagic fever, and 24,000 deaths caused by Dengue per year.[2] "Overall, it is estimated that in 2001 dengue was responsible for … 653,000 Disability-Adjusted Life Years (DALYs)".[3] The cost of dengue over the past 10 years in Puerto Rico alone has been $250 million.[4] By implementing an effective Dengue control policy, lives could be saved, morbidity could be reduced and money could be saved.

Description of the vector

The Aedes Aegypti mosquito transmits the dengue virus. Humans and mosquitoes are the primary hosts. In Africa and Asia the virus is thought to be sustained by vertical transmission in mosquitoes and amplified in other primates between human epidemics.[2] This mosquito is an efficient vector for the virus. It lives in close proximity to humans and feeds primarily on human blood. It feeds during the day (early morning and late afternoon), its' bite is rarely noticed by humans and it can feed repeatedly during one life cycle.[3]

Because the mosquito is active both indoors and outdoors during the day, people have difficulty avoiding it, and interventions like bed nets are not helpful. In Asia and America it breeds primarily in manmade receptacles, however in Africa it breeds in natural water sources as well.[3] However, this is not the only vector capable of carrying and infecting humans with Dengue. The *Aedes albopictus* has been incriminated in a recent outbreak in Hawaii and is an increasingly common inhabitant of the continental US.[4]

Description of the disease

Dengue is caused by four closely related flaviviruses (DEN-1, DEN-2, DEN-3, DEN-4). These four viruses are antigenically distinct and do not grant the victim cross-immunity (infection with DEN-1 protects against future infection with DEN-1, but not DEN-2, a patient could be infected 4 times, once with each serotype). In fact, secondary infection (infection with a different serotype) raises the likelihood of a severe form of Dengue infection, dengue hemorrhagic fever.[2]

The signs and symptoms of Dengue fever include "high fever, frontal headache, retro-orbital pain, myalgias, arthralgias, vomiting, and often a maculopapular rash."[4] Symptoms may range from unnoticeable to debilitating. Treatment for this form of the disease is supportive. Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) are more severe and potentially fatal forms of the disease.[4]

Patients may appear to have classic Dengue Fever at the beginning of this disease, however, when the fever subsides after 2-7 days "the patient may become restless or lethargic, show signs of circulatory failure, and experience hemorrhagic manifestations."[4] These hemorrhagic manifestations may include petechia, ecchymoses, purpura, bleeding from mucosa, etc. and may be demonstrated by a positive tourniquet test. The tourniquet test consists of inflating a blood pressure cuff around a patient's arm for five minutes and monitoring for the occurrence of petechiae.[5]

To be diagnosed with Dengue Hemorrhagic Fever (DHF) the patient must have a platelet count less than 100,000/mm3 and objective evidence of increased vascular permeability. DHF may then lead to Dengue shock syndrome (DSS), characterized by pulse pressure less than 20 mm Hg or hypotension.[2] There is no specific treatment for DHF/DSS. Depending on diagnostic acumen and availability of intravenous fluids and blood for treatment of the hypovolemic shock the mortality rate ranges from less than 1% to greater than 30% for DHF/DSS.[5]

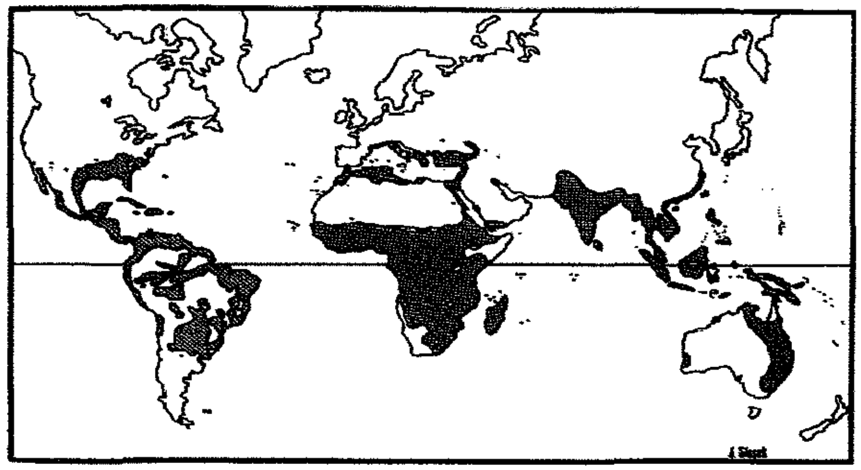
Most cases of primary infection with the dengue virus produce mild symptoms or no symptoms at all. Symptoms of dengue fever caused by a primary infection are usually worse in older children or adults than in young children, however children are more susceptible to DHF/DSS during a secondary infection.[6]

History of Dengue and Early Control Efforts

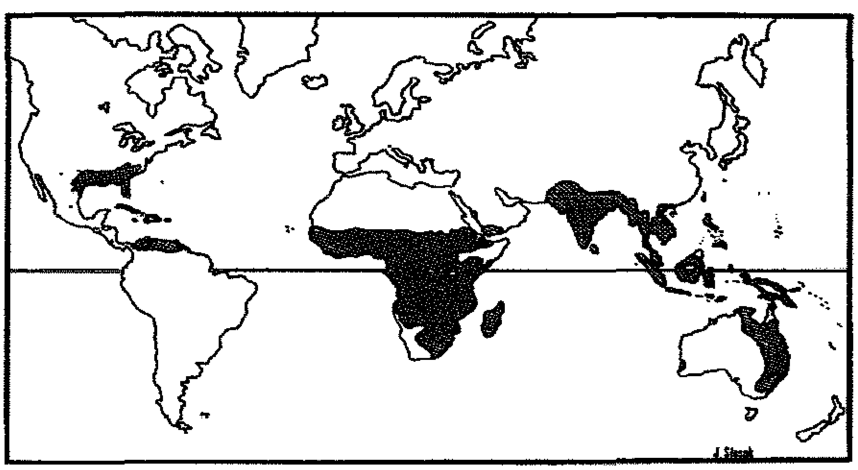
In order to have a better understanding of this disease and its potential for being controlled as well as its potential for causing harm, it is helpful to examine the history of the disease. This section of the paper will describe the history of the vector and the disease and the successes and failures of control efforts.

History of the Aedes Aegypti

In order to understand the distribution of this disease it is important to understand the history of this mosquito. By most accounts the mosquito originated in Africa, feeding on primates and reproducing in small areas of water, like holes in trees and crab burrows. The mosquito adapted to reproduce in small manmade water receptacles and feed primarily on human blood. Beginning with the slave trade in the 1500s the mosquito began breeding in water storage containers of shipping vessels and with this new form of transportation invaded other parts of the world. By 1930, with the help of human transportation, the mosquito had spread to almost all the geographic locations it's biology would allow. This is a map of the probable distribution of the vector at that time.[7]



The mosquito population began to plummet during the 1900s when eradication programs began. The mosquito was determined to be associated with yellow fever and dengue and the PAHO began to focus efforts on eradicating this species to prevent disease. During this time the US focused limited attention on this vector. Partially due to efforts to control malaria by breeding site destruction and pesticide use in the US and through strong efforts by other western hemisphere countries to eradicate yellow fever and dengue, the mosquito population dropped and dengue ceased to be a significant problem in the US.[7] This map shows the vector distribution at its lowest point in 1970.[7]



The US officially stopped efforts to control Aedes Aegypti and eradication was discontinued completely in 1970. Other countries in the Western hemisphere began to decrease efforts to control the vector as well and the mosquitoes began to re-infest areas where it had previously been eradicated. At the present time the distribution of the vector is above the pre-intervention level.[4]

History of Dengue Illness

Dengue illness has been recognized and written about for the past 200 years, although the illness has only been associated with its' mosquito vector for the past 70 years.[8] Epidemics were first reported in 1779-1780. These epidemics occurred in Asia, Africa, and North America. In the beginning these epidemics caused little mortality and epidemics were infrequent, occurring every few decades.[9]

Following World War II a global pandemic of dengue began. With the continued increase in world travel, dengue strains began to effect different regions of the world and the virus reached a state of hyperendemicity in many regions. Hyperendemicity describes a state in which multiple serotypes of the virus are circulating in the same region. As can be reasoned from the previous discussion, this creates a very dangerous environment in which people become at risk for multiple infections with different virus serotypes and ultimately, dengue hemorrhagic fever (DHF). The first known epidemic of DHF occurred in 1953 in the Philippines and marks the turning point in the history of the dengue virus. At this time the virus switched from a relatively benign infectious agent to a major cause of morbidity and mortality.[9]

During the next 20 years epidemics of dengue hemorrhagic fever spread throughout Southeast Asia and became one of the leading causes of hospitalization and death for children in this region. During the same period of time however, dengue was not active in the Americas, because the vector had been temporarily eradicated. In the 1970s the situation changed. The vector began to repopulate the Americas and Pacific Islands and with the vector came the virus. During the 1980s and 1990s DHF epidemics arrived to many countries in the Western Hemisphere that had never before experienced this form of the disease.[9]

Over the past twenty years dengue has become an increasing problem. There are several factors that are thought to be responsible for this increase. The first factor is global population growth. With this dramatic growth in the human population has come a dramatic increase in substandard housing and poorly managed water, waste and sewage. People living in these conditions often gather clean water when it is available in as many containers as possible. Along with an increased production of items like tires and manmade plastic containers and a lack of garbage removal, these factors have provided a new abundance of small areas of standing water that make perfect breeding sites for mosquitoes. All of these factors together lead to a large population of humans in close proximity to each other and to mosquito breeding sites. This is the perfect environment for dengue transmission.[9]

Another factor that may have contributed to the increase in dengue incidence is the ineffective control methods that have been used. During the

1970s through the 1990s the control method most commonly used was space spraying with insecticide. This method killed adult mosquitoes, but had little lasting effect on the mosquito population. Also, it gave people a false sense of security that the mosquito problem was being treated and people in endemic areas stopped participation in helpful control efforts like removing and emptying water containers that served as mosquito breeding sites.[9]

In addition, over the past several decades air travel has continued to increase making it difficult to contain dengue serotypes. Also, lack of resources in dengue endemic regions has led to a decay of public health infrastructure making it difficult for countries to respond to epidemics in an effective way.[9]

Future trends

The phenomenon of global warming is predicted to have a profound effect on the distribution of dengue and its vector. The WHO has predicted that a temperature increase of 1-2 degrees Celsius would increase the population at risk by several hundred million and fatalities by 20,000-30,000.[6] It is also estimated that the factors mentioned above that have led to an increase in dengue incidence (i.e.: increase in air travel, increase in plastic containers) will continue to contribute to the problem in the coming decades.[9] With past failures to control the disease in mind, and bleak predictions for expansion of the disease in the future, finding the best policy for dengue control for the present is vital.

Current Policies to Control Dengue

Gubler et al[1] presented the following policies for dengue virus control in Puerto Rico in 1991: "Aedes Aegypti eradication, ultra-low-volume (ULV) insecticide application, regulation of air travel, development and use of dengue vaccines, preventive measures keyed to improved surveillance, and routine mosquito control efforts." The program proposed by Gubler et al[1] has five components based on the last two options. These components are: 1. proactive surveillance 2. rapid-response emergency vector control 3. long-term, integrated community-based mosquito control 4. education of the medical community 5. an emergency hospitalization plan. The purpose of this proposed program would be to reduce dengue incidence and thus reduce the likelihood of DHF/DSS cases in Puerto Rico.[1]

Since publication of the 1991 article, the two policies most extensively researched, and the most widely advocated solutions to the dengue problem are vaccination and long-term, integrated community-based mosquito control. However, a safe and effective vaccine for dengue is not currently available for human use. For this reason, recent research on dengue vaccines will be briefly reviewed, including information on the current status and predictions for the future. The remainder of the paper will be devoted to an in-depth analysis of long-term, integrated community-based mosquito control, because this is the policy currently available and most widely recommended. This paper will systematically review the research on this latter policy and evaluate the feasibility, cost effectiveness, acceptability, effectiveness and sustainability of the policy as defined by recent research.

Methods

Criteria

The criteria used to evaluate the policy included feasibility, cost effectiveness, acceptability, effectiveness and sustainability.

Method for Finding Information

Information sources

CDC website, CDC Faculty (Gubler and Clark), Medline, article reference lists.

Search Strategy for Background

Searched with Medline MESH terms: Dengue and limited to English review articles for general background; used Dengue MESH term with subheading prevention and control limited to English for vector control background. Search included articles published from 1985 to the present, March 2005. Also, the CDC and WHO websites on Dengue were used.

Search Strategy for Results

Search Strategy for Vaccine Section

Searched Medline using MESH terms: "Dengue" and "Vaccine". This search was limited to the English language and included articles published from January 2004 to the present, March 31, 2005. This search was limited to include only the most recent articles. Articles were reviewed for relevance to the current topic and eleven of the nineteen articles are cited in this paper.

Also, the CDC website on Dengue and the WHO website on Dengue were used as sources of information for this section.

Search Strategy for Vector Control Section

Searched with Medline MESH terms: "Mosquito Control"[MeSH] AND "Dengue/prevention and control"[MeSH]. This search was limited to articles written in the English Language and published between January 1, 1991 AND March 14, 2005.

This search yielded 95 articles. Articles that focused on the efficacy of specific insecticides, the behavior or biology of mosquitoes, vaccination or Dengue outbreaks among tourist were excluded by title.

The 74 articles remaining were reviewed by title, abstract and full article to evaluate for internal validity using the following four selection criteria:

1. Population: Were study participants or communities in a Dengue endemic region like Puerto Pico? (i.e.: not tourists).
2. Study intervention: Did at least one study community or group participate in a long-term integrated community-based vector control program or a component of such a program?
3. Control intervention: Was there a comparison group that received no intervention? If not was there a comparison intervention?
4. Outcome: Was one of the outcomes measured feasibility, cost effectiveness, acceptability, efficacy or sustainability? Was efficacy measured in terms of reduction in morbidity or mortality from Dengue? Or was there a secondary marker such as mosquito count or increased knowledge?

Nine articles met the four inclusion criteria outlined above. Although the best evidence would have been randomized controlled trials of this program in comparison to no intervention, this level of evidence was limited and other levels of evidence needed to be included in order to evaluate this program. In the results section of this paper I will review the information given in these nine articles and discuss the quality of evidence provided.

Results

In this section of the paper I will briefly discuss development and use of dengue vaccines. I will then discuss the vector control policy proposed by Gubler in 1991, long-term integrated community-based mosquito control. Based on research conducted from 1991 to the present, I will determine how this policy meets the criteria I have chosen: feasibility, cost effectiveness, acceptability, sustainability, and efficacy. The following outlines how this results section will be structured.

I. Development and use of Dengue Vaccines

- **A. Why vaccine development is a problem**
- **B. Review of recent progress made in vaccine research**
- **C. Predictions about vaccine availability in the future**

II. Long-term integrated community-based mosquito control

- **A. Definition of integrated community-based mosquito control**
- **B. Review of research**
    1. **Swaddiwudhipong**
    2. **Swaddiwudhipong**
    3. **Lloyd**
    4. **Espinoza-Gomez**
    5. **Madeira**
    6. **Kay**
    7. **Winch**
    8. **Sanchez**
    9. **Kay**

C. Table of Evidence

I. Development and use of dengue Vaccines

Gubler et al[1] stated: "Ultimately, prevention of epidemic DHF may depend on vaccination. At the present, however, no vaccines against dengue viruses are available for general use." The article goes on to speculate that a safe vaccine for dengue would not be available for at least ten years.[1] Fourteen years after the publication of this article I will briefly review the progress made on vaccines for dengue and discuss why this option is not currently possible and when it is predicted to be available.

I. A. Why vaccine development is a problem

There are some attributes of the Dengue Viruses that make vaccination appear feasible. First of all the infection is not chronic in humans. After a short period of viremia (3-7 days) normal hosts develop lasting immunity to the serotype of the virus with which they have been infected. So, in the 1940s a live attenuated vaccine was created that could produce a protective immune response in humans.[10]

There have been vaccines created for each of the four serotypes of dengue, but it has proven difficult to create a combined tetravalent vaccine that will have lasting protection against all four serotypes. Tetravalent formulations created so far would require many dosages and do not appear practical to administer.[10]

As discussed in the history section Dengue Hemorrhagic Fever is a new disease that was first described in the 1950s. So although the vaccines tested in the 1940s proved to be effective at preventing classic Dengue fever, it is unknown whether the vaccines will prevent the more dangerous DHF. Studies performed since that time have used animals, however, there is no animal model of DHF.[10]

The exact mechanism is unclear, but as mentioned earlier, secondary infection is a major risk factor for DHF. For example, someone who has had a mild dengue infection caused by DEN-1 and developed immunity to this serotype has a much greater risk of developing the hemorrhagic form of the disease when infected with DEN-2 than someone who is infected with DEN-2 with no previous history of dengue infections.[10]

Although the exact mechanism is unclear, it appears that immunity to one serotype is the risk factor. So creating dengue immunity by vaccination may actually increase a person's chance of developing DHF.[11] This theoretical likelihood of DHF increases if immunity to all four serotypes is not complete and lasting. This aspect of the disease makes it extremely important that patients receive the full, effective dose of the vaccine, and considering that the highest risk population lives in resource poor regions, makes the challenge even more difficult.[10]

I.B. Review of recent work on Vaccine development

Despite the limitations to vaccine development there has been a great deal of support for this endeavor. In an editorial published in January 2004, Deen[12] discusses the $55 million dollar grant donated to the Pediatric Dengue Vaccine Initiative (PDVI) by the Bill and Melinda Gates Foundation and how the funds may best be used to expedite the extensive safety and efficacy research that must be done before a vaccine can be approved for use. Deen[12] also acknowledges that even with funding for research available there must also be resources to fund the manufacture and distribution of the vaccine to the people who need it. He calls for research to be done on cost effectiveness of a Dengue vaccine, hoping the results of such research will attract the interest of the pharmaceutical industry to produce such a drug and compel resource poor nations to set aside funds for acquiring the vaccine once it is produced.[12]

Indeed, a study on the cost effectiveness of such a vaccine was performed by Shepard et al[13] and published in 2004. In this study a cost-effectiveness model was developed to determine if a pediatric tetravalent dengue vaccine given at 15 months of age to children in Southeast Asia would be economically feasible. The model assumed there would be two doses and an effective vaccine would decrease morbidity and mortality by 89%. These estimates lead to a prediction of cost per DALY of US$ 50 for vaccination. The article compares this figure to a vector control program in Singapore that created a cost of US$ 3139 per DALY. This estimated cost has many hypothetical components, but it does offer evidence that if a safe, effective, moderately priced vaccine becomes available it could offer financial relief to dengue endemic countries.[13]

There are currently several vaccine candidates being developed. The first I will discuss is a live-attenuated vaccine containing all four serotypes (tetravalent). The virus was attenuated by passage through primary dog kidney cells (PDK). In a double blind randomized controlled trial published in 2004, Sabchareon et al[14] studied the safety and immunogenicity of this vaccine in Thai schoolchildren ages 5 to 12 years.[14]

This study was designed after several other studies on healthy adult and child volunteers had been performed using one and two doses of the vaccine. This study tests two different formulations of the vaccine given as a three dose series. There were 103 children used for this study. The study showed a high rate of seroconversion to all four viruses. Also, there was a moderate amount of reactivity to the vaccine that the authors believe should be improved.[14]

Two interesting ideas were supported by this study. First, reactivity to the vaccine was less in younger children. Because primary infection with Dengue is usually mild in young children and worsens with age, it is plausible that reactions to a live-attenuated vaccine would be less in younger children.[14]

Secondly, the study was conducted in Thailand where dengue has a high incidence and study participants were likely exposed to the wild virus. During this study there were no cases of DHF. This provides a small amount of evidence that the vaccine is not predisposing the children to DHF.[14] A study performed by Guy et al[15] also supports the safety of this vaccine. In this study an assay was used to test vaccinated children and controls for Antibody Dependent Enhancement (ADE). This is thought to be one of the causes of DHF. Children who were vaccinated with the tetravalent vaccine did not show significant ADE, suggesting that the vaccine had not increased their risk of developing DHF.[15]

This vaccine was only tested on children who were antibody negative for flaviviruses. It is unclear how children previously exposed to one of the viruses would react to the vaccine. This will be an important question to answer in the future because a large percentage of the population in Dengue endemic regions have exposure to one or more of these viruses.[14]

A new vaccine has been developed with recombinant DNA methods using a clone of the cDNA from DEN-4. This vaccine is a live-attenuated virus with a genetic deletion.[16] In a recent placebo-controlled phase two trial performed by Durbin et al the vaccine was well tolerated and immunogenic when given in one dose. This live-attenuated virus also seems limited in its ability to infect mosquitoes, so there is a reduced risk of it being propagated and reverting to a virulent virus.[17]

It is hoped that this virus can be used as a backbone to create vaccines for the other three serotypes. It is unknown at this time if a tetravalent vaccine of this kind will be as successful as this monovalent vaccine. This was an excellent study that provides strong evidence for safety and immunogenicity in healthy adults in a non-endemic region. However, the participants were only followed for 42 days so additional follow-up and studies are needed.[17]

The third type of vaccine candidate is a chimera that uses the backbone of the yellow fever vaccine virus with a substitution of the prM and E proteins with heterologous dengue proteins of all four serotypes.[18] This is possible because all viruses are in the *Flaviviridae* family. In a study of multiple formulations of tetravalent vaccines of this kind, the vaccine proved safe, immunogenic and effective when challenged with the wild virus in monkeys. This vaccine was administered in one dose, and 92% of the monkeys were protected from dengue when challenged post vaccination. Work is needed to determine if the immunity is lasting, as well as determine long-term safety.[19]

Recombinant proteins are a third option for Dengue vaccines. In two recent articles by Hermida et al, DEN-1[20] and DEN-2[22] proteins were combined with a meningicoccal protein called P64k. When administered to mice these proteins elicited a strong neutralizing antibodies and proved effective and protecting mice from a dengue inoculation challenge. The authors report that a vaccine of this kind would be economical to produce. Further studies are needed to determine if vaccines of this kind would provide lasting immunity and be safe to use in primates and humans.[22]

Another possibility is a DNA vaccine. Although several are mentioned in the review literature[22], no articles concerning these vaccines were found in this search.

I.C. Predictions

There are multiple predictions about the future of Dengue vaccines, however, there is little concrete evidence to support these predictions. In a recent editorial by Edelman[23] the author gives an informative review of vaccination literature and then states as an expert in this field, "I am optimistic that field trials of 1 or more dengue vaccines will commence within 3 years in Latin America and in Southeast Asia."

The WHO website on dengue predicts that a vaccine will be ready for human use in the next few years.[3] The CDC's predictions are less optimistic. A recently updated Dengue Website predicts five to ten years before a vaccine will be ready for human use.[4]

Although these estimates vary the fact remains that there is no vaccine currently available, and the question becomes where should energy be focused now?

II. Routine mosquito control programs in the form of long-term integrated community-based vector control

Gubler et al[1] state, "Ultimately, prevention of epidemic dengue and DHF/DSS will depend upon effective, long-term mosquito control." The evidence at the time suggested that the only way to achieve this goal would be through "Integrated community-based vector control". Programs that were run by the central government had failed due to lack of support and participation of the community and loss of governmental funding between epidemics.[1]

IIA. Definition of Integrated community-based vector control

An Integrated-community based vector control program involves educating and encouraging the public to act on eight major points: "1. DHF/DSS is now endemic in Puerto Rico and the US Virgin Islands; 2. The islands are at high risk of epidemic DHF/DSS because of the high *Ae. aegypti* densities in all major cities; 3. most dengue transmission occurs in and around the home; 4. this happens because people accumulate excessive trash around their homes, thereby creating mosquito breeding places; 5. dengue can be prevented by controlling these domestic larval habitats, but only the people involved can effectively clean up the areas around their homes to prevent mosquito breeding; 6. control must be a community effort, because mosquitoes can fly from house to house; 7. insecticide spraying is expensive, is ineffective for routine mosquito control, and at most should only be used in emergency situations; and 8. it is the responsibility of the people, not the government, to prevent epidemic DHF/DSS in Puerto Rico and the U.S. Virgin Islands. Educational materials have been created by medical anthropologists, social scientists, and health educators to communicate these points effectively to Puerto Rico's diverse population.[1]

IIB. Review of Research

The following is an analysis of the research performed on this policy since the time of the publication of the 1991 article.

1. The first article obtained through the methods described above was a study published in 1992 conducted by Swaddiwudhipong et al[24] in an urban area of Thailand. An intensive control program was initiated in 1988 and studied for a two-year period. The program consisted of an educational curriculum involving lectures and discussions for health care personnel, government officers, school children, teachers and people in the community in community gathering places like temples and Rotary Clubs.[24]

The classes described the severity of dengue and what people needed to do in their own homes to remove mosquito breeding sites. Similar information was included in a simultaneous mass media campaign. At the same time Temephos a larvicidal chemical was made available at a low cost and ULV spraying twice a year continued by the government to kill adult mosquitos.[24]

In order to evaluate the program *Aedes* larval surveillance was conducted in March 1988 before the program began and again in June 1988. The survey included every other house in randomly selected sections of the community.[24]

In 1989 and 1990 twice a year health workers accompanied by school children conducted home visits. The visits were conducted in March and June and during the visits community members were taught about the severity of Dengue and how to remove or treat larval breeding sites. *Aedes* larval surveys were conducted in and around the homes at the time of the visit and one and a half months later.[24]

This article reports several larval indices. It reports percentage of houses with Aedes larvae, percentage of containers with larvae, and the Breteau index (number of larval containers per 100 houses). It also reports on the number and kind of containers in the homes. This article does not give statistical analysis of the data.[24]

This article does show that a community-based intervention is feasible and sustainable for two years. Also, the larval indices used in this study are sited in the literature as valid and useful secondary markers of success of a program. Because a community based program takes time to effect mosquito count, and even longer to effect Dengue morbidity and mortality, secondary markers such as larval indices and assessments of community Dengue knowledge, attitude and practices (KAPs) are recommended to monitor the success of the program.[25]

However, it is unclear whether the changes in the indices are statistically significant, so effectiveness of the program cannot clearly be determined. Cost effectiveness is also not discussed. All indices seem to decrease during 1990 suggesting to the authors that during the year of a major outbreak people were more likely to eliminate breeding sites.[24]

This study may have been improved by offering statistical analysis of the indices collected. Also, it has been mentioned in the literature that ULV spraying is not effective and offers communities a false sense of security which in turn discourages people from participating in breeding site removal.[25] This may be occurring in this intervention as well, because the one year that spraying decreased due to lack of governmental funds, fewer breeding sites were found. This was the same year as a significant outbreak of DHF occurred in this area, so it is unclear which was the motivating factor.

2. In a follow-up report by Swaddiwudhipong et al[26] a survey of knowledge, attitude and practices was performed on the community that received the educational program described above. The survey was given to 417 women chosen from every other household in a randomly selected section of the community. The survey was performed 6 weeks after the first home visit.[26]

The majority of respondents knew one or two symptoms of Dengue, that it is transmitted by *Aedes* mosquitoes, and that these mosquitoes bite during the day. Also, most respondents believed that they were personally responsible for preventing Dengue in their homes and could name several common household breeding sites that should be eliminated or treated. This offers some evidence that a community-based program is acceptable to people given that one of the core principles is for the community to take responsibility for the program.[26]

The majority of these respondents had 6 years or less of education. Despite limited education the women were still able to understand and repeat the key concepts of this educational campaign. This offers some weak evidence that such a campaign would also be feasible in Puerto Rico, where the average educational level is higher. Also, this region is similar to Puerto Rico in that the mosquito breeding sites are mostly manmade containers (unlike Africa where mosquitoes breed in crab boroughs). If strong evidence becomes available to suggest that this program is effective, the information may be helpful in developing a plan for Puerto Rico.

3. In a study conducted by Lloyd et al[27] in 1992 a community-based communication program created to teach residents in Merida, Yucatan, Mexico how to eliminate larval production sites proved to be effective. This study was implemented in six communities, and communities were randomized to treated or untreated control groups. The communities were evaluated before intervention, immediately after intervention, and six months post-intervention. Significant improvements in the knowledge and behavior of the intervention group were found at both post-intervention evaluations.[27]

The Breteau index (number of positive containers/100 houses surveyed) remained unchanged for the intervention group while it significantly increased for the control group. The authors conclude that this was most likely due to the decrease in trash collection services available in the community. So, the intervention group was working hard to minimize the accumulation of breeding sites around their homes (usually disposable containers), but had trouble disposing of sites that were already present.[27]

Even though the Breteau index is considered a valid measurement, the index in this intervention program remained unchanged in the intervention group. It would be expected that a true behavior change in participants would lead to a reduction in breeding site. However the lack of increase in comparison to the controls and the increased knowledge does suggest that this intervention is somewhat effective, and the results that were sustained at the six-month time point suggests that it may also be sustainable. The study was well designed and controlled.[27]

This study offers strong evidence that educational campaigns can change knowledge about Dengue vectors, however the amount of success in behavioral change appears limited by the lack of community services, like garbage collection. Also, in a report of the methods used to develop and implement this program the authors report few difficulties in gaining the support and participation of the community and completing the project within four months.[28] This offers strong evidence that the intervention is both feasible and currently acceptable to a DHF endemic community. There was no information on costs.

4. In 2002 spraying with ultra low volumes (ULV) of malathion was still a widely recommended and practiced form of vector control. Espinoza-Gomez et al[29] developed a study to evaluate the effect of an integrated community-based vector control campaign for reducing breeding sites, and compare its effect with those obtained by ULV spraying of malathion.[29]

The study was a randomized community trial in Colima, Mexico. The communities were randomized to one of four conditions: educational campaign alone, ULV malathion spraying alone, both treatments simultaneously, or no treatment. Assessments were performed before the interventions began and six months post-intervention and consisted of an entomological survey and a KAP survey of each house.[29]

The educational campaign group had significantly greater reduction in larvae positive breeding sites than the ULV spraying only group and the combined education and spraying group. The authors concluded that the ULV spraying might have lessoned the positive effect of the educational campaign in the combined intervention, perhaps due to a false sense of security provided by chemical spraying. The KAP scores did not differ between groups, suggesting that this survey of knowledge, attitude and practices may not be a helpful indicator of success of a program.[29]

This study is well designed and well controlled and offers strong evidence that a community based educational campaign can be effective at reducing breeding sites. It offers weak evidence about sustainability. The effects were seen at six months post intervention, but at no time points in the future. The authors report no difficulties with gaining support and participation from the community suggesting it is feasible and acceptable, but give no information about costs.[29]

5. In an article by Madeira et al[30] an educational campaign performed in fifth and sixth graders in Brazil was evaluated. The intervention consisted of four

fifty-minute didactic activities over the course of two weeks. There was a significant increase in knowledge about dengue and control measures in the intervention group when compared to controls. The authors site past examples of how school children were instrumental in motivating communities to control filarial and chagas diseases and predict that the same process could occur with Dengue.[30]

This article offers evidence that knowledge may be increased, but gives no evidence that this has had any effect on behavior in the community. There is no evidence concerning sustainability or cost effectiveness. The authors mention no problems gaining the support and participation of the children in these activities, so it appears that it is feasible and acceptable. However, assessments at future time points and indicators of behavioral changes would be helpful in determining the utility of this intervention.[30]

6. Kay et al[31] studied the effect of an integrated community-based control program in Vietnam. Out of ten communes, six were chosen based on high dengue incidence to participate in the intervention and the other four were used as the control group. The interventions involved treatment of permanent water containers with Mesocyclops species (predacious cyclopoids that feed on mosquito larvae), educational programs for the community and home visits, recycling incentives to encourage the disposal of manmade containers, and community cleanup projects.[31]

At the end of the study the *Ae. Aegypti* population in the six treated communes ranged from 0 to 0.3% of the total population before the intervention.

The vector population in the four control communes at the end of the study ranged from 14.4 to 367.0% of the original population. It was difficult to determine how these results affected the level of dengue transmission during this time. Dengue is often asymptomatic in children and people in these communities were resistant to having blood samples collected.[31]

This study provided strong evidence that a community-based vector control can be effective at eradicating vectors from dengue endemic regions. This study also provided two-year follow up data that provided strong evidence that the program was sustainable. Also, the authors mention that they received political and community support for the program, and has been implemented in many other communities in Vietnam. This provides evidence that it is feasible and acceptable. However there was no information about costs. This study could have been improved by randomizing communities and conducting proactive surveillance to determine if the dengue transmission rate is affected as well.[31]

7. In a study conducted in Puerto Rico by Winch et al[32] several components of a community based program were evaluated using KAP surveys, larval indices, focus groups and interviews. The intervention consisted of televised public service announcements and posters, educational programs for elementary and pre-school children, and an exhibit at a children's museum.[32]

Exposure to the programs was associated with increased dengue knowledge, and to a lesser degree, increased performance of dengue prevention behaviors like covering tires, and slightly lower indices of mosquito infestation. This study provides evidence that this kind of intervention involving children may be effective at changing the behavior of parents may be effective. Randomizing participants may have increased the strength of the evidence. It provides strong evidence that the programs are feasible and acceptable, but no evidence about costs or sustainability was presented.[32]

8. In recent articles the definition of integrated long-term community based control has changed somewhat. Instead of a program that must be the responsibility of the community to finance and maintain a slightly different approach, called "intersectoral coordination" is advocated. The activities used for vector control are still the same, involving education and activities to dispose of or treat mosquito breeding sites, but responsibility, funding and planning includes sources outside the community. Sanchez et al[33] states the following, "sustained dengue control requires partnerships among donors, the public sector, civil society, non-governmental organizations, and the private for profit sector, and the interlinking of politicians, administrators, engineers, urban planners, sanitarians and environmental groups into intersectoral teams."

Despite these changes, the activities, control practices, and need for community participation remains unchanged, so intersectoral coordination programs will be included in this section.

In a recently published article Sanchez et al[33] reports on a pilot project that involves intersectoral coordination in Cuba. The community was involved in all levels of planning and implementation of this intervention, but in addition an intersectoral team was created to help plan and implement the program. A community similar to the one receiving the intervention was defined as the control. The interventions consisted of eliminating unused containers in houses and surrounding areas, covering water tanks and cleaning neighborhoods and public areas. In the control area the national dengue control program continued to be carried out without input from the community or other sectors outside the government. A KAP survey and collection of larval indices were collected from both groups before and after the one-year intervention.[33]

This study found that knowledge about breeding sites and dengue symptoms increased significantly, and House Index (number of containers with larvae/number of all containers *100) decreased significantly in the intervention community while there were no significant changes in the control group.[33]

This study offers evidence that a community-based program with the addition of intersectoral coordination may be effective. Including multiple communities randomized to intervention and control groups could have strengthened the evidence. The project is feasible and accepted by the community. There is no information about costs. The intervention was sustained for one year, which is a longer period of time than most studies, and gives some evidence that the program is sustainable.[33]

9. The final article in this review was published in February 2005 by Kay et al[34] and is a follow-up report to a previously reviewed study. The previously described community based vector control program studied in Vietnam. The program was expanded to include 37 communes with complete eradication of *A. aegypti* in 32 of these communes and very low mosquito populations in the other 5. There have been no cases of dengue detected in the treated communes since

2002 despite rates as high as 112.8 per 100,000 in the surrounding untreated communes.[34]

At the end of this article the authors state that additional research will be performed this year to evaluate cost effectiveness but state that the estimated cost of the program is 20 cents per person year. It is unclear what this figure means in terms of DALYs so the evidence concerning cost effectiveness is inconclusive at this time. However, this article provides strong evidence that this intervention is effective at reducing mosquito population, and most likely dengue morbidity and mortality as well. It also provides strong evidence that the program is sustainable and acceptable to the communities.

C. Table of evidence for long term community-based vector control

Weak evidence to support + **Weak evidence against -**

Moderate evidence to support ++ **Moderate evidence against - -**

Strong evidence to support +++ **Strong evidence against - - -**

Article	Current Feasibility	Cost effective	Acceptable to people	Sustainable	Effectiveness
1. Swaddiwudhipong	+			+	
2. Swaddiwudhipong			+		+
3. Lloyd	+++		+++	+	+
4. Espinoza-Gomez	+++		+++	+	+++
5. Madeira	+++		+++		
6. Kay	+++		+++	+++	+++
7. Winch	+++		+++		++
8. Sanchez	+++		+++	+	++
9. Kay	+++	+	+++	+++	+++

<u>Discussion</u>

<u>Vaccination</u>

Vaccination could potentially be a cost-effective method of dengue virus control, and many countries are interested in obtaining a tetravalent vaccine. A vaccination campaign would be easier to implement than vector control, and has been a very attractive option to donors. This review showed that recent advances have been made in vaccine-related research. However, a safe and effective tetravalent vaccine for dengue has not been developed and may not be available for years to come. Dengue presents a unique challenge to vaccine developers, in that antibodies to the disease are a major risk factor for the hemorrhagic form of the disease. It is still unclear to what degree and for how long immunity must last to protect patients from the disease without increasing the risk of DHF.

All vaccine trials to date have been performed on healthy controls with no previous exposure to viruses in the *Flaviviridea* family. Large proportions of the populations in dengue endemic regions are already seropositive for these viruses. Vaccine safety and efficacy have not been demonstrated in HIV-positive patients, who comprise a large proportion of the population in the regions most affected by dengue.[23] .

Questions remain regarding ethical issues in vaccine testing. Is it acceptable to administer a vaccine that may increase the chances of DHF? For patients that have already received the vaccine (i.e.: Thai children) how long should investigators wait before the vaccine is considered safe to use? Some have suggested that DHF may still be a risk twenty years after initial exposure. Should entire populations be vaccinated after five years of safety testing? Also, if a vaccine does become available, is it safe to discontinue vector control programs? And if so, will herd immunity be enough to break the transmission cycle and protect those in whom vaccination is contraindicated? These issues may cause as many limitations on vaccine development as the current technological barriers.

Long term integrated community-based vector control

Evidence

A review of the recent literature on long-term integrated community-based vector control programs provides evidence that this policy is feasible, acceptable to communities, sustainable, effective at lowering the mosquito population, and probably effective at reducing morbidity and mortality from dengue.

The one limitation for this policy may be cost-effectiveness. There is little evidence about the costs of this program. The ongoing analysis in Vietnam will help determine the overall cost-effectiveness of a vector control program. It could be harmful to waste valuable resources on a program that does not prove to be cost-effective.

Also, it will be helpful to follow the long-term incidence, morbidity and mortality of dengue in the Vietnamese communities. Dengue epidemics only occur every few years, so the apparent absence of the disease for several years, although promising, is not conclusive evidence that the disease might have been eradicated.

Generalizability

Even though many of these studies were performed in places other than Puerto Rico, there are many similarities among these different locations. For example, the communities in Vietnam have dealt with water shortages. Most participants in the study communities have water piped into their homes and store water in large containers to save for times of shortage. These containers are one of the primary sources of breeding sites. Since the same problem occurs in Puerto

Rico,[32] the program that has been so successful and sustainable in Vietnam may also be effective in Puerto Rico.

Although the same copepod and larvivorous fish that were used in Vietnam are not indigenous to Puerto Rico, the same process of testing and treating water sources with larvicidal species or chemicals can be used.

Also, the educational level in Puerto Rico is higher than that of many of the communities studied in the programs reviewed above and baseline level of dengue knowledge is already high in Puerto Rico.[32] This suggests that some of the obstacles that had to be overcome in communities in Mexico and Vietnam, may not be problems in Puerto Rico. Perhaps more effort and resources can be devoted to mobilizing people rather than educating them. For example, incentives can be offered for recycling containers and neighborhood cleanups can be organized.

Secondary Findings

Over the past fourteen years it was discovered that the policy of long term integrated community vector control could be made more successful by adding input from other sectors. Some problems required intervention by local, state and national governments. For example, some behaviors like storing water and accumulating trash around homes were being driven by water shortages and lack of garbage collection services. In Puerto Rico, a successful vector control program will require input from the community as well as the government.

Studies in the past have shown that ULV spraying in places like Puerto Rico neither reduces the mosquito population long-term, nor reduces the incidence of dengue infection.[35] In this review, it was shown that ULV spraying actually decreased the effectiveness of the community-based program.

Implications

From the evidence presented here, the best policy for the reduction of morbidity and mortality caused by dengue virus infection in Puerto Rico is a policy that includes long-term integrated community vector control as desribed by Gubler,[1] with the addition of governmental input and support. This policy has the best chance of providing protection from dengue for all of Puerto Rico's citizens. Furthermore, all routine ULV spraying should be discontinued to increase the effectiveness of this program and to decrease costs.

To test the effectiveness of this policy for the first several years, larval indices would be most helpful. Data indicate that knowledge, attitude and practices (KAP) survey scores do not always correlate with actual behavior. When the program is successful at eliminating the mosquito population, dengue morbidity and mortality should be followed as an indicator of success.

Although costs and simplicity may make vaccination appear to be an attractive option, it is important to focus resources on the policy that is currently safe, feasible, acceptable, sustainable and effective.

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